Published in final edited form as:

J Allergy Clin Immunol. 2015 January ; 135(1): 267–269.e14. doi:10.1016/j.jaci.2014.07.035.

Bacterial metabolites of diet-derived lignans and isoflavones inversely associate with asthma and wheezing

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Keywords

Lignans; Isoflavones; Asthma; Wheezing; Enterolactone; O-Desmethylangolensin; NHANES; Microbiome

To the editor:

Lignans and isoflavones are plant-derived chemicals with potent anti-inflammatory and anti-oxidant effects¹. Lignans are ubiquitous in Western diets with flaxseeds containing the greatest amounts, while isoflavones are most abundant in soybeans (Table E1). The end product(s) of gut microbial metabolism of lignans is enterolactone²; metabolism of the isoflavone daidzein gives rise to equol and o-desmethylangolensin (O-DMA). Human studies demonstrate inverse associations between lignans and isoflavones and hormone-dependent cancers, cardiovascular disease, and osteoporosis¹, and improvements in asthma control are reported in those with high soy consumption³. Experimental studies suggest that bacterial metabolites of isoflavones attenuate allergic airway inflammation,⁴ however similar studies are unavailable for enterolactone.

Prospective human studies demonstrate that microbial exposures are important for asthma development and control⁵, but the mechanism of this association is unclear. Given their anti-inflammatory and anti-oxidative properties, we hypothesized that bacterial metabolites of lignans and isoflavones may mediate the beneficial effects of bacteria on asthma and lower airway disease. To provide evidence supporting our hypothesis, we conducted a cross-sectional population-based study using data from the National Health and Nutrition Examination Survey (NHANES), which collected urinary levels of lignan and isoflavone metabolites and medical history of asthma and wheeze.

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Data were obtained from the 2003–2004, 2005–2006, 2007–2008, and 2009–2010 NHANES. 9,633 subjects ages 6–85 had complete data for the primary analyses of the association between urinary levels of lignan and isoflavone metabolites (e.g. enterolactone, equol, and O-DMA) and physician-diagnosed current asthma and self-reported non-asthmatic wheeze, adjusting for age, gender, race/ethnicity, log-transformed urinary creatinine level, poverty index ratio (PIR), and body mass index (BMI). We performed three different sensitivity analyses: A. adjusting for smoke exposure (we adjusted for presence of household smoke exposure among subjects <20 years old and never, former, or current smoking status among subjects ≥20 years old), B. adjusting for plant intake (using total dietary fiber intake), and C. stratifying each analysis by atopic status (presence or absence of allergen-specific IgE, available in 2005–2006 only). Statistical analyses were performed with STATA12.0 (College Station, TX) using the sampling and weighting variables provided by NHANES. See this article's Online Repository for additional methods (www.jacionline.org).

Participants reporting current asthma were more likely to be female, younger, African American, aeroallergen sensitized, and have a PIR less than 1. Those reporting non-asthmatic wheeze were more likely to be older and Caucasian. Current asthmatics were more likely to report being former smokers, and those with non-asthmatic wheeze were more likely to be current smokers or have household smoke exposure. Asthma and wheeze status was positively associated with BMI (Table E2). Urinary levels of bacterial metabolites by tertile are presented in Table E3. These levels varied by race/ethnicity, PIR, age, BMI category, and tobacco exposure status (Tables E4–E8). NHANES participants were selected at random for urinary lignan and isoflavone analysis. The sample with data available on urinary bacterial metabolite measurements was similar to the general NHANES population, although more adults (82% vs. 72%, $P = <0.001$), and more subjects with BMI greater than 30 (29% vs. 26%, $P = <0.001$) composed the subsample (Table E9).

Urinary enterolactone levels were inversely associated with current asthma (Table I, Figure 1). In logistic regression models adjusted for race/ethnicity, PIR, gender, age, creatinine, and BMI, the odds ratio (OR) for current asthma for the highest tertile of urinary enterolactone was 0.69 (95% CI 0.56–0.85). Levels of urinary enterolactone and O-DMA were inversely associated with non-asthmatic wheeze. The OR for non-asthmatic wheeze for the highest tertile of urinary enterolactone was 0.53 (95% CI 0.42–0.67). The OR for non-asthmatic wheeze for the highest tertile of urinary O-DMA was 0.64 (95% CI 0.52–0.80). In a model including all metabolites, urinary enterolactone remained independently inversely associated with current asthma, while both enterolactone and O-DMA remained independently inversely associated with non-asthmatic wheeze (Table E10).

In sensitivity analyses, the inverse association between isoflavone and lignan metabolites and current asthma and non-asthmatic wheeze remained significant after the addition of smoke exposure to the models, stratifying by age (Tables E11–12). Adjustment for total dietary fiber intake, a global measure of plant intake, led to minimal change (0–3%, data not shown) in the point estimates for the association between enterolactone and current asthma, and enterolactone and O-DMA and non-asthmatic wheeze. There were similar associations

between enterolactone and O-DMA and current asthma and non-asthmatic wheeze when the outcomes were stratified by atopic status (data not shown).

We examined the relationship between bacterial metabolites of dietary lignans and isoflavones and asthma and wheeze using a large, nationally representative sample. We hypothesized that these metabolites would be inversely associated with asthma and wheezing because of their effects on molecular pathways involved in allergic inflammation and oxidation, and limited human studies supporting an association⁶. We found that higher urinary levels of the lignan metabolite enterolactone was inversely associated with a physician diagnosis of current asthma, and both enterolactone and O-DMA were inversely associated with non-asthmatic wheezing within the last year. Our findings were similar among adults and children and robust to smoke exposure, fiber intake, and atopic status. These results suggest that interventions to increase levels of enterolactone and O-DMA may be beneficial in the prevention and treatment of asthma and non-asthmatic wheeze.

Several epidemiologic and laboratory-based studies have demonstrated associations between bacterial flora and lower respiratory disease⁷. The presence of specific organisms and the diversity of microflora are thought to be relevant in this relationship⁵. Notably, bacteria of the genus *Bacteroides* which are positively correlated with lignan metabolism, are inversely associated with the development of allergy, while the presence of *Clostridium*, which is negatively correlated with lignan metabolism, is positively associated with the development of allergy^{8,9}. These observations together with our findings suggest that the bacterial metabolites of lignans and isoflavones, in particular enterolactone, may have a causal role in disease prevention and control.

Our study has several limitations including incomplete characterization of respiratory outcomes and cross-sectional studies such as this are only a starting point for identifying causal relationships between exposures and disease. Further research will be necessary to determine if our observations result from different dietary choices among those with and without lower respiratory disease, that we could not detect by adjusting for fiber. Although lignan and isoflavone metabolites have antioxidant, anti-inflammatory, and other biological activities which we hypothesize underlie their association with lower respiratory disease, these may be biomarkers of another causal factor rather than themselves being causal in disease amelioration. Nonetheless, treatment with other (non-metabolite) lignans such as macelignan and honokiol decreases Th2-mediated pulmonary inflammation in animal models of asthma, supporting our overall hypothesis⁴.

In summary, we have identified significant concentration-dependent associations between bacterial metabolites of diet-derived lignan and isoflavone metabolites and asthma and wheezing in a large, nationally-representative population-based sample. To our knowledge, this is the first report of an association between biologically active bacterial metabolites and lower respiratory outcomes in a nationally-representative population. Future clinical and laboratory-based studies are needed to support a causal relationship between lignan and isoflavone metabolites and lower respiratory disease. The potential diagnostic or therapeutic role for these bacterial metabolites, in particular enterolactone, warrants further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by grants from The American Academy of Allergy, Asthma and Immunology and FARE and a KL2 Medical Research Investigator Training award (an appointed KL2 award) from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award 1KL2 TR001100-01) to JHS, NIH grant T32AI07306-24, and a generous contribution from the Vinik Family. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health.

Abbreviations

(O-DMA)	O-Desmethylangolensin
(NHANES)	National Health and Nutrition Examination Survey
(PIR)	Poverty Index Ratio
(OR)	odds ratio
(BMI)	Body Mass Index

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Clinical Implications

Bacterial metabolites of diet-derived lignans and isoflavones were inversely associated with asthma and wheezing. They may influence the development and control of lower respiratory disease.

Figure 1. Predicted probability of current asthma (A), and non-asthmatic wheeze (B) with 95% CIs by urinary enterolactone levels.

Table I

Odds ratios (and 95% CI) for current asthma and non-asthmatic wheeze by level of urinary metabolites of lignans and isoflavones

Metabolite	Tertile	Current Asthma		Non-Asthmatic Wheeze	
		Crude OR	Adjusted OR*	Crude OR	Adjusted OR*
Enterolactone	1	1.0 [REF]	1.0 [REF]	1.0 [REF]	1.0 [REF]
	2	0.59 (0.47–0.74)	0.61 (0.48–0.78)	0.64 (0.48–0.86)	0.67 (0.49–0.90)
	3	0.63 (0.52–0.76)	0.69 (0.56–0.85)	0.52 (0.34–0.65)	0.53 (0.42–0.67)
	Test for trend (p-value)	<0.001	<0.001	<0.001	<0.001
O-DMA	1	1.0 [REF]	1.0 [REF]	1.0 [REF]	1.0 [REF]
	2	1.03 (0.86–1.23)	1.06 (0.88–1.28)	0.79 (0.63–1.00)	0.79 (0.62–1.00)
	3	0.94 (0.77–1.23)	1.00 (0.80–1.26)	0.63 (0.51–0.79)	0.64 (0.52–0.80)
	Test for trend (p-value)	0.82	0.98	<0.001	<0.001
Equol	1	1.0 [REF]	1.0 [REF]	1.0 [REF]	1.0 [REF]
	2	0.97 (0.79–1.20)	1.01 (0.81–1.26)	1.15 (0.94–1.41)	1.12 (0.91–1.40)
	3	1.08 (0.90–1.30)	1.15 (0.93–1.43)	0.94 (0.76–1.16)	0.95 (0.76–1.18)
	Test for trend (p-value)	0.39	0.18	0.56	0.57

OR, Odds ratio; CI, Confidence interval.

* Adjusted for age, gender, race/ethnicity, log-transformed urinary creatinine, poverty index ratio, and BMI.